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Adherence and plasma HIV RNA responses to highly active antiretroviral therapy among HIV-1 infected injection drug users

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Abstract

Background: The benefits of highly active antiretroviral therapy (HAART) for the treatment of HIV infection are well documented, but concerns regarding access and adherence to HAART are growing. We evaluated virological responses to HAART among HIV-1 infected patients who were injection drug users (IDUs) in a population-based setting where HIV/AIDS care is delivered free of charge.

Methods: We evaluated previously untreated HIV-1 infected men and women who initiated HAART between Aug. 1, 1996, and July 31, 2000, and who were followed until Mar. 31, 2002, in a province-wide HIV treatment program. We used Kaplan–Meier methods and Cox proportional hazards regression in our evaluation of time to suppression (i.e., less than 500 copies/mL) and rebound (i.e., 500 copies/mL or more) of plasma HIV-1 RNA, with patients stratified according to whether or not they had a history of injection drug use.

Results: Overall, 1422 patients initiated HAART during the study period, of whom 359 (25.2%) were IDUs. In Kaplan–Meier analyses, the cumulative suppression rate at 12 months after initiation of HAART was 70.8% for non-IDUs and 51.4% for IDUs ($p < 0.001$) (these values include people who achieved suppression before 12 months but who might not have been followed for the full 12-month period). Among patients who achieved suppression of plasma HIV-1 RNA, the cumulative rebound rate at 12 months after initial suppression was 23.8% for non-IDUs and 34.7% for IDUs ($p < 0.001$). However, after adjustment for adherence and other covariates, the rates of HIV-1 RNA suppression (adjusted relative hazard 0.9, 95% confidence interval [CI] 0.7–1.0) and HIV-1 RNA rebound (adjusted relative hazard 1.3, 95% CI 1.0–1.6) were similar between non-IDUs and IDUs. Differences between non-IDUs and IDUs were even less pronounced in subanalyses that considered only therapy-adherent patients ($p > 0.1$).

Interpretation: Non-IDUs and IDUs had similar rates of HIV-1 RNA suppression and rebound after the initiation of HAART, once lower levels of adherence were taken into account. Nevertheless, the lower virological response rates among IDUs suggest that, unless interventions are undertaken to improve adherence, these patients may experience elevated rates of disease progression and use of medical services in our setting.

The benefits of triple-drug highly active antiretroviral therapy (HAART) in the management of HIV disease are well established. Through the suppression of plasma HIV-1 RNA, HAART has been shown to improve CD4 cell counts and in turn to decrease morbidity and mortality rates among HIV–infected patients.[1,2] As a result, HAART has become the standard of care for HIV-infected patients.[3]

In North America, these findings have emerged amid growing concerns about inequitable access to antiretroviral therapy and lower levels of adherence among those who were infected during later stages of the HIV epidemic, particularly illicit injection drug users (IDUs).[4-6] In British Columbia, the majority of HIV infections among IDUs did not occur until 1996,[7] and hence the bulk of HIV-infected IDUs will only be starting to require HIV treatment over the next several years.[3,8] An earlier analysis from our setting suggested that IDUs had rates of HIV-1 RNA suppression similar to those of non-IDUs when adherence was taken into account.[9] However, this earlier work did not report rates of failure to achieve HIV-1 RNA suppression among IDUs, nor did it report rates of HIV-1 RNA rebound.

Since that time, little work has been done to calculate population-level estimates of the proportion of IDUs initiating HAART and their virological responses to therapy. Because a growing number of IDUs will soon be at risk of HIV-related illness and death in many settings,[4-6] it is critical to evaluate virological outcomes among IDUs who have presented for antiretroviral therapy. Therefore, we undertook the present study to characterize all HIV/AIDS patients who have initiated HAART in the province of British Columbia since 1996 and to evaluate virological response to treatment among patients with and without a history of injection drug use.

Methods

The dispensing of antiretroviral medications in British Columbia has been described in detail elsewhere.[10,11] In brief, the HIV/AIDS Drug Treatment Program of the BC Centre for Excellence in HIV/AIDS remains the only source of free antiretroviral medications in the province, and less than 1% of HIV-infected British Columbians receive antiretrovirals from other sources.[10] In June 1996 the Centre adopted antiretroviral therapy guidelines based on

plasma viral loads, consistent with those put forward by the International AIDS Society-USA.[12] The Centre's guidelines were revised in July 1997 to recommend triple-drug therapy for anyone with plasma HIV-1 RNA levels greater than 5000 copies/mL or CD4 cell counts below 500 cells/mL who had not previously received antiretroviral therapy.[13] The Centre's HIV/AIDS Drug Treatment Program has received ethical approval from the University of British Columbia's Ethics Committee for Human Experimentation at its St. Paul's Hospital site, and the program conforms with the province's *Freedom of Information and Protection of Privacy Act*.

All HIV-infected men and women in the current study were entered into the HIV/AIDS Drug Treatment Program when they received their first prescription for antiretroviral agents. Any physician enrolling an HIV-infected person must complete a drug request enrolment form, which acts as a legal prescription and supplies baseline information, including past HIV-specific drug history, CD4 cell count, plasma HIV-1 RNA level, current drug prescriptions and data about the enrolling physician. At the time of the first refill, participants are asked to complete a survey, which elicits information on sociodemographic characteristics. The treating physicians are also asked to complete a clinical staging form that uses the World Health Organization clinical staging system.[14] Thereafter, participants complete annual surveys on a volunteer basis. In the present study, we evaluated all HIV-1 infected men and women who had not taken antiretrovirals previously and who were first prescribed triple-drug antiretroviral therapy between Aug. 1, 1996, and July 31, 2000. The patients were followed until Mar. 31, 2002.

As an initial analysis, we evaluated the baseline demographic and clinical characteristics of patients with and without a history of injection drug use. This variable was defined on the basis of self-reports (through the annual participant survey) and through physician reports. To be conservative in our analysis, we considered any positive report of this risk behaviour at any time during follow-up indicative of a history of injection drug use. The categorical explanatory variables described below were analyzed with Pearson's χ^2 test, and continuous variables were analyzed with the Wilcoxon rank-sum test.

We then evaluated time to suppression of plasma HIV-1 RNA after initiation of the first HAART regimen. As previously,[9,15] suppression was defined as the first of at least 2 consecutive measurements of plasma HIV-1 RNA level of less than 500 copies/mL. Those who never achieved suppression were censored at the date of the last measurement of HIV-1 RNA before Mar. 31, 2002. Patients who achieved an HIV-1 RNA level of less than 500 copies/mL only once were not considered to have achieved suppression and hence were not included in this analysis.

We also evaluated the time to rebound of plasma HIV-1 RNA after initial virological suppression below 500 copies/mL. This analysis included any patient who achieved at least one RNA measure below 500 copies/mL. As previously,[15] rebound of HIV-1 RNA was defined as the first of 2 consecutive measurements of plasma HIV-1 RNA level of 500 copies/mL or more after any measurement of less than 500 copies/mL. To be conservative, the rebound event was assumed to occur at the midpoint date between the last HIV-1 RNA measurement of less than 500 copies/mL and the first of the 2 consecutive measurements at least 500 copies/mL. For consistency with previous studies we evaluated only patients who experienced RNA suppression before 32 weeks after the initiation of therapy.[15] Patients who experienced suppression but not rebound were censored as of Mar. 31, 2002, or, if follow-up ended before this date, as of the last HIV-1 RNA measurement.

For the 2 treatment outcomes (suppression and rebound), cumulative event rates were estimated by Kaplan–Meier methods.

Cox regression was then used to calculate univariate and adjusted relative hazards (RHs) and 95% confidence intervals (CIs).[16] The assumption of proportional hazards was validated by inspection of log (–log [survival function]) estimates against log time plots. We derived population-based estimates for the overall cohort and then, in subanalyses, examined adherent patients only.

The following salient baseline prognostic variables were examined: date of initiation of therapy, adherence, sex, age, use of protease inhibitor in the initial HAART regimen, prior clinical diagnosis of AIDS, physician experience, CD4 cell count, and log_{10}-transformed plasma HIV-1 RNA level. We adjusted for the date of therapy initiation (on or after v. before July 31, 1997) in all multivariate analyses because this was the date when British Columbia's therapeutic guidelines for antiretroviral therapy were changed to recommend universal use of triple-drug regimens. The definition of adherence was based on the ratio of the period that the total amount of medication dispensed to the patient would last to the follow-up period during the first year on therapy, expressed as a percentage.[17] We have previously demonstrated how this estimate strongly predicts virological response and mortality rate, and how it can be used to adjust for the potentially confounding effect of treatment interruption.[9,18,19] Patients were defined a priori as nonadherent if they received antiretroviral medications for less than 95% of the follow-up period during the first year of therapy, as in previously published work.[18] The definition of physician experience was also selected a priori on the basis of previous findings.[20,21]

For the multivariate analyses, we examined variables hypothesized a priori to be associated, either clinically or behaviourally, with virological response. These variables were first examined in univariate analyses to determine unadjusted RHs. Any variables associated with an event (suppression or rebound) in these univariate analyses ($p < 0.05$) were then entered into a fixed model. In addition, initial HAART regimen, baseline HIV-1 RNA level and CD4 cell count were entered into the final model because of their known relation to clinical and virological response.[11,22] All tests of significance were 2-sided, with a p value of less than 0.05 indicating that an association was statistically significant.

Results

Between Aug. 1, 1996, and July 1, 2000, a total of 1583 participants who had never received antiretroviral therapy and who were 18 years of age or older began triple-drug therapy, consisting of 2 nucleoside reverse transcriptase inhibitors plus either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. Of these, 161 (10.2%) were excluded from this analysis because one or both of the baseline CD4 cell count and plasma HIV-1 RNA level had not been determined within 6 months before the start of the antiretroviral therapy. Those excluded from this analysis were more likely to be younger ($p = 0.04$) and taking protease inhibitors ($p = 0.02$). In the study population, 359 (25.2%) patients were identified as having a history of injection drug use, and 1063 (74.8%) were identified as non-IDUs.

Table 1 shows the results of univariate statistical comparisons of baseline clinical and sociodemographic characteristics. IDUs were less likely to be at least 95% adherent ($p = 0.001$), to be male ($p = 0.001$), to have a baseline clinical diagnosis of AIDS ($p = 0.026$) and to have a physician with

HIV-related experience (p = 0.015). Conversely, IDUs were more likely to have received a protease inhibitor in the initial regimen (p = 0.026) and to have a higher CD4 cell count (p = 0.002). We detected no statistical difference between IDUs and non-IDUs with regard to date of therapy initiation, age and baseline HIV-1 RNA level.

We observed marked differences between IDUs and non-IDUs in time to HIV-1 RNA suppression, as indicated by Kaplan–Meier estimates of the cumulative suppression rate for all patients (Fig. 1, left). The cumulative suppression rate at 12 months after initiation of HAART was 70.8% for non-IDUs and 51.4% for IDUs (log-rank, p < 0.001) (these values include people who achieved suppression before 12 months but who might not have been followed for the full 12-month period). However, a subanalysis showed that among the 816 patients (656 non-IDUs and 160 IDUs) who were defined as adherent, there was no difference between IDUs and non-IDUs in terms of HIV-1 RNA suppression (log-rank, p = 0.12) (Fig. 1, right).

History of injection drug use was also strongly associated with lower rates of HIV-1 RNA suppression in univariate Cox regression analyses (RH 0.6, 95% CI 0.5–0.7). However, similar to our earlier analyses,[9] rates of HIV-1 suppression were similar between non-IDUs and IDUs (adjusted RH 0.9, 95% CI 0.7–1.0) in a multivariate Cox model that adjusted for adherence, sex, age, protease inhibitor use, baseline CD4 cell count, HIV-1 RNA level and date of therapy initiation. In this model, adherence was strongly associated with suppression (adjusted RH 4.4, 95% CI 3.8–5.1). Similarly, injection drug use was not significant (adjusted RH 0.9, 95% CI 0.7–1.1) in subanalyses restricted to the 816 patients who were defined as adherent.

We also observed marked differences between IDUs and non-IDUs in time to HIV-1 RNA rebound, as indicated by Kaplan–Meier estimates of the cumulative rebound rate for the 970 patients who achieved HIV-1 RNA suppression, defined as less than 500 copies/mL at least once during follow-up (Fig. 2, left). Among patients who

Table 1: Baseline characteristics of patients initiating highly active antiretroviral therapy (HAART)

Characteristic	Group; no. (and %) of patients*		
	Non-IDUs $n = 1063$	IDUs $n = 359$	p value
Date of initiation of therapy			
Before July 31, 1997	259 (24.4)	103 (28.7)	
On or after July 31, 1997	804 (75.6)	256 (71.3)	0.10
Adherence			
≥ 95%	656 (61.7)	160 (44.6)	
< 95%	407 (38.3)	199 (55.4)	0.001
Sex			
Female	139 (13.1)	85 (23.7)	
Male	924 (86.9)	274 (76.3)	0.001
Age			
Median (and IQR)	37.1 (31.9–44.0)	37.6 (32.3–43.0)	0.75
Use of protease inhibitor†			
No	345 (32.5)	94 (26.2)	
Yes	718 (67.5)	265 (73.8)	0.026
Baseline AIDS diagnosis			
No	914 (86.0)	325 (90.5)	
Yes	149 (14.0)	34 (9.5)	0.026
Physician's HIV-related experience‡			
≤ 5 patients	240 (22.6)	104 (29.0)	
≥ 6 patients	821 (77.4)	255 (71.0)	0.015
Baseline CD4 cell count (cells/μL)			
Median (and IQR)	260 (120–410)	290 (140–460)	0.004
Plasma HIV-1 RNA, copies/mL (log$_{10}$)			
Median (and IQR)	5.1 (4.6–5.5)	5.1 (4.6–5.5)	0.49

Note: IDU = injection drug user (any report of injection drug use at any time during follow-up), IQR = interquartile range.
*Except where otherwise indicated.
†Use of protease inhibitor in the initial HAART regimen.
‡When patient was enrolled in the treatment program.

achieved suppression of HIV-1 RNA, the cumulative rebound rate at 12 months after initial suppression was 23.8% for non-IDUs and 34.7% for IDUs (log-rank, $p < 0.001$). However, a subanalysis showed that among the 716 adherent patients (577 non-IDUs and 139 IDUs) there was no difference between IDUs and non-IDUs in terms of HIV-1 RNA rebound (log rank, $p = 0.12$) (Fig. 2, right).

In univariate Cox regression analyses, IDUs had more rapid HIV-1 RNA rebound rates in univariate analyses (RH 1.5, 95% CI 1.2–1.9) (Table 2). However, as with suppression, the differences between IDUs and non-IDU were less pronounced in multivariate analyses (adjusted RH 1.3, 95% CI 1.0–1.6), with adjustment for adherence, sex, age, protease inhibitor use, baseline CD4 cell count, baseline HIV-1 RNA level and date of therapy initiation (Table 2). In this analysis, adherence was highly protective against HIV-1 RNA rebound (adjusted RH 0.3, 95% CI 0.2–0.3). As with HIV RNA suppression, history of injection drug use was also nonsignificant (adjusted RH 1.2, 95% CI 0.8–1.6) when this model was restricted to the 716 patients who were defined as adherent.

Interpretation

We found that IDUs had markedly lower rates of plasma HIV-1 RNA suppression, and, among patients who achieved any HIV-1 RNA suppression, IDUs had markedly higher rates of rebound. However, these differences were explained by lower levels of adherence to HAART among the IDUs; the virological responses for the 2 groups were similar in adjusted analyses and restricted analyses that considered only adherent patients.

Several studies have demonstrated that the amount of HIV RNA circulating in the plasma is directly related to HIV disease progression,[23–25] and our data indicate that IDUs in our setting will likely experience more rapid disease progression because of lower rates of virological response. However, we also found that the lower rates of virological response to HAART were primarily driven by lower levels of adherence among IDUs. Strategies that have helped to improve access and adherence to antiretrovirals among HIV-infected IDUs include directly observed therapy programs, access to medical services without appointment, on-site pharmacists at medical clinics and improved access to addiction treatment.[26–32] Conversely, lower levels of HIV-related experience among physicians have been associated with worse access to therapy.[31]

With regard to tracking disease progression, the main limitation of the present study is that we examined only patients who actually initiated triple-drug therapy during the study period. To put the scale of this concern into perspective, consider that approximately 30% of the province's 5000 to 15 000 IDUs have HIV infection,[33,34] of
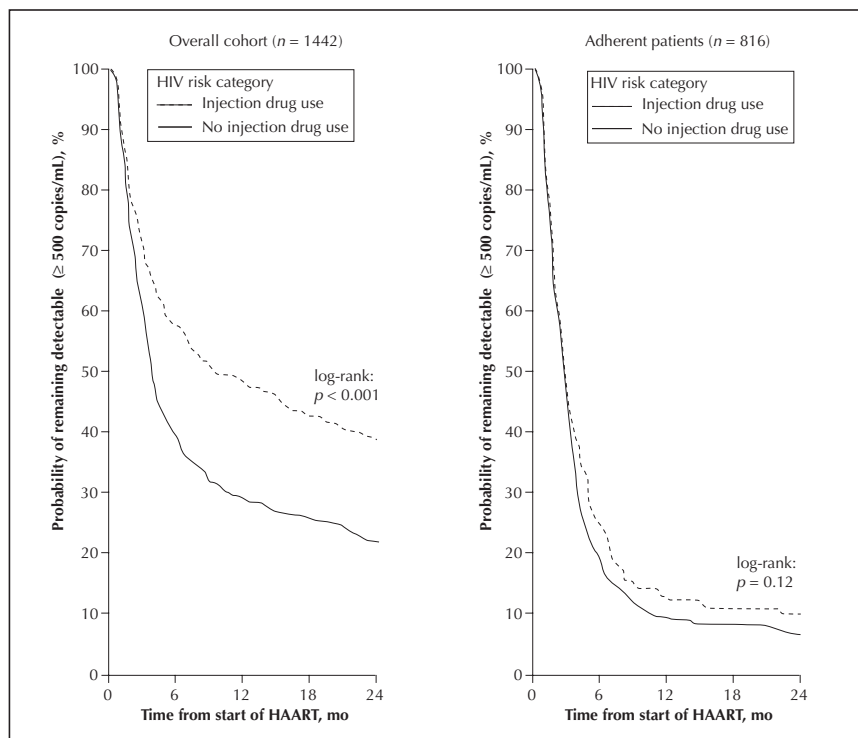

Fig. 1: Kaplan–Meier estimates of cumulative rates of suppression of plasma HIV RNA within the entire cohort of 1422 patients who initiated highly active antiretroviral therapy (HAART) during the study period (at left) and within the subpopulation of 816 patients who were defined as adherent (at right), according to history of injection drug use.

whom only 359 initiated triple-drug therapy during this period. Other limitations, which probably resulted in strong conservative biases in our analyses, are the fact that injection drug use is a stigmatized behaviour that may be underreported by IDUs and the fact that some patients with a history of injection drug use might have become abstinent during follow-up.[35] Similarly, people who use non-injection illicit drugs, such as crack cocaine, may be at similar risk of poor adherence to HAART,[36] but these were included in the comparison group in the present study. In addition, although using refill compliance as a measure of adherence has been previously validated,[9,17–19] there might have been differences in adherence levels between IDUs and non-IDUs, even among patients who were defined as adherent;[35] this again represents a conservative bias. Finally, because we do not have population-based data on coinfection with hepatitis C, this variable could not be evaluated in the present study.[21]

In summary, we found that IDUs had markedly lower rates of virological suppression and higher rates of virological rebound. Because much of the difference in virological response rates is explained by lower levels of adherence to HAART, programs that have been shown to improve adherence with antiretroviral therapy, such as addiction treatment strategies,[32,37] should be expanded. Our findings have implications for public health and medical service use be-

cause, given what is known about the HIV epidemic among IDUs in British Columbia,[7,33,34] we can expect that IDUs will soon be experiencing high levels of illness and death as a result of lower levels of adherence with therapy.

Table 2: Cox proportional hazards analyses of the time to HIV RNA rebound among previously untreated patients who started HAART between Aug. 1, 1996, and July 31, 2000

Variable	Type of analysis; relative hazard (and 95% CI)*	
	Unadjusted	Adjusted†
HIV risk group (IDU v. non-IDU)	1.5 (1.2–1.9)	1.3 (1.0–1.6)
Adherence (≥ 95% v. < 95%)	0.2 (0.2–0.3)	0.3 (0.2–0.3)
Sex (male v. female)	0.7 (0.6–1.0)	1.1 (0.8–1.4)
Age (per 10-yr increase)	0.8 (0.8–0.9)	0.9 (0.8–1.0)
Initial HAART (PI v. NNRTI)	1.1 (0.9–1.4)	1.2 (0.9–1.5)
CD4 cell count, cells/μL (per 100-cell increase)	1.1 (1.0–1.1)	1.1 (1.0–1.1)
HIV-1 RNA, copies/mL (per $\log_{10}$ increase)	1.0 (0.8–1.1)	1.1 (1.0–1.3)

Note: CI = confidence interval, PI = protease inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor.
*Relative hazard values for which the CI does not cross 1.0 are significant at the α = 0.05 level.
†Adjusted for adherence, sex, age, PI use, baseline CD4 cell count, baseline HIV-1 RNA and date of therapy initiation.
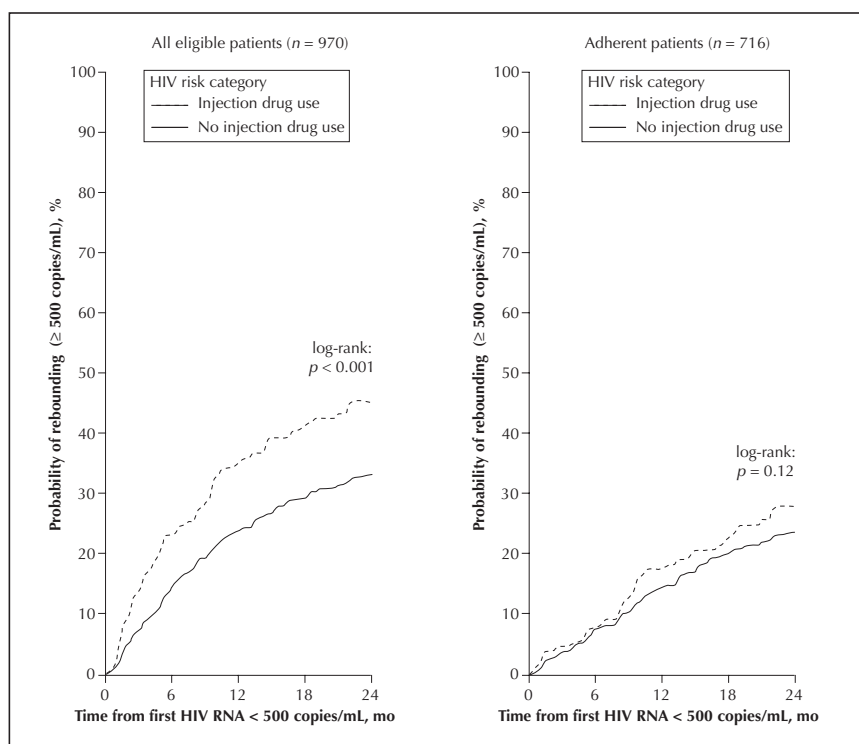

Fig. 2: Kaplan–Meier estimates of cumulative rates of rebound of plasma HIV RNA within the cohort of 970 patients who achieved suppression of HIV RNA (defined as viral count of less than 500 copies/mL at least once) during follow-up (at left) and within the subpopulation of 716 patients who were defined as adherent (at right), according to history of injection drug use.

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